Garvin, S. Alessi, J. Laydon, J. Kropp, and E. Webb for technical assistance.

Registry No. 1, 64997-22-4; 2, 24736-19-4; 3, 97059-60-4; 3·HBr, 66659-52-7; 4, 97059-61-5; 4·HBr, 66659-64-1; 5, 87532-36-3; 5·HBr, 66659-77-6; 6, 97059-62-6; 6·HBr, 66659-63-0; 7, 64997-47-3; 7·HBr, 66659-53-8; 8, 66659-61-8; 8·HBr, 97059-63-7; 9, 66659-81-2; 9·HBr, 78631-68-2; 10, 64997-34-8; 10·HBr, 66659-76-5; 11, 78643-32-0; 11·HBr, 66659-97-0; 12, 65823-24-7; 13, 97059-65-9; 13·HBr, 97059-64-8; 14, 78631-67-1; 14·HBr, 66659-78-7; 15, 66659-79-8; 16, 97059-67-1; 16·HBr, 97059-66-0; 17, 78631-71-7; 17·HBr, 66660-01-3; 18, 66659-94-7; 18·HBr, 66659-95-8; 19, 97059-68-2; 19·HCl, 66659-56-1; 20, 66659-84-5; 21, 78631-69-3; 21·HBr, 66659-92-5; 22, 78631-70-6; 22·HBr, 66659-99-2; 23, 66659-87-8; 24, 92754-18-2; $24 \cdot {}^{3}/_{2}$HBr, 97059-69-3; 25, 66659-72-1; 26, 65823-25-8; 27, 66659-73-2; 28, 66659-74-3; 29, 78631-66-0; 29·$HClO_4$, 97059-70-6; 30, 66659-54-9; 31, 66659-85-6; 32, 66659-86-7; 33, 66659-88-9; 34, 66660-02-4; 35, 66660-07-9; 36, 66660-03-5; 37, 97059-71-7; 38, 97059-72-8; 39, 97059-74-0; 39·HCl, 97059-73-9; 40, 66660-04-6; 41, 97059-75-1; 42, 97059-76-2; 43, 97059-77-3; 44, 97059-78-4; 45, 97059-84-2; 45·HCl, 97059-79-5; 46, 67645-07-2; 47, 39908-38-8; 48, 23908-75-0; 49, 49855-26-7; 50, 97059-80-8; 51, 62894-32-0; 52, 97059-81-9; 53, 21224-34-0; 54, 39908-69-5; 55, 66659-98-1; 56, 66660-00-2; 57, 97059-82-0; 58, 66660-06-8; 59, 73648-78-9; 60, 66659-69-6; 61, 66659-83-4; Ia, 51490-06-3; Ib, 6266-57-5; Ic, 1023-17-2; Id, 66659-59-4; Ie, 51490-05-2; If, 2132-57-2; Ig, 38803-55-3; Ih, 3141-93-3; Ii, 4927-55-3; Ij, 29955-23-5; Ik, 366-68-7; Il, 1979-63-1; Im, 2729-19-3; In, 36187-57-2; Io, 7150-10-9; Ip, 3669-47-4; Iq, 66659-90-3; IIa, 27895-95-0; IIb, 1484-50-0; IIc, 57297-30-0; IId, 1889-77-6; IIe, 66659-60-7; IIf, 51324-24-4; IIg, 42445-10-3; IIh, 66659-80-1; IIi, 56913-16-7; IIj, 66659-96-9; IIk, 5653-07-6; III, 2632-13-5; IIm, 71006-38-7; IIn, 27895-96-1; VIa, 42445-18-1; VIb, 4720-82-5; VIc, 7467-90-5; VId, 4254-18-6; VIe, 1218-85-5; VIf, 66659-65-2; VIg, 5702-73-8; VIh, 6706-96-3; VIi, 6706-95-2; VIj, 5653-60-1; 2-aminothiazoline, 1779-81-3; 1,2-dibromoethane, 106-93-4; pivalic anhydride, 1538-75-6; 5-ethylthiourea, 2986-20-1; thiourea, 62-56-6; 2-bromo-1-phenyl-2-(3,4-dimethoxyphenyl)ethanone, 66659-93-6; α-(trimethylsilyl)oxy-β-[3,4-dimethoxyphenyl]styrene, 97059-83-1; bis(3-fluoro-4-methoxy)benzoin, 66659-67-4; 3-fluoro-4-methoxybenzaldehyde, 351-54-2; bis(3-fluoro-4-methoxy)desoxybenzoin, 1827-54-9; 4,4′-bis(methylsulfinyl)benzoin, 66660-05-7.

Acylmorphinans. A Novel Class of Potent Analgesic Agents

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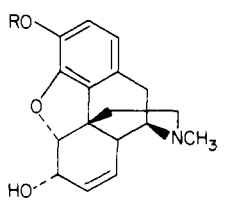
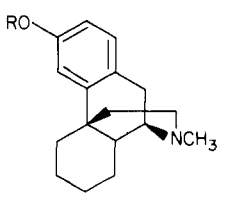
A series of novel 2- and 3-acylmorphinans (8–14) was synthesized in our search for a potent analgesic agent with low addiction potential. The compounds were evaluated for antinociceptive potency and receptor binding affinity. Among these compounds, the levorotatory 3-acetyl-*N*-(cyclopropylmethyl)morphinan (**12**) was found to be an orally active analgesic, comparable in potency to morphine (**1**), yet only weakly able to substitute for morphine (**1**) in morphine-dependent rats.

The importance of the phenolic hydroxyl group in enhancing both antinociceptive potency as well as opiate receptor affinity of morphine (**1**) and structurally related compounds is well-known.[1] However, substances having such a polar group often have poor oral activity, due to poor absorption and rapid metabolic inactivation via the phenolic hydroxyl group. In an attempt to reduce inactivation and prolong activity, we have already reported[2] the preparation of metabolically stable 3-*O*-*tert*-butylmorphine (**3**) and (−)-3-*tert*-butoxy-*N*-methylmorphinan (**6**). Unfortunately, these potentially interesting analogues



1, R=H
2, R=CH_3
3, R=$C(CH_3)_3$



4, R=H
5, R=CH_3
6, R=$C(CH_3)_3$

of codeine (**2**) and levomethorphan (**5**) were not only marginally active as analgesics but were also unstable under acidic conditions. In our search for novel substituents that might be able to replace the vulnerable phenolic group in morphinans and that would give stable analgesics, we focused our attention on replacement of the phenolic hydroxyl by an acyl substituent. Most importantly, it was speculated that the acyl group might interact with the opiate receptor in a mode that is different from that of the phenolic morphinans and thus eliminate or reduce the undesirable side effects common to the phenolic type of analgesics, while increasing the oral effectiveness of these compounds. In view of these assumptions, we carried out the synthesis of structurally novel 2- and 3-acylmorphinans (**8–14**).

Chemistry. The starting material, (−)-*N*-methylmorphinan (**7**), was prepared by the Grewe method.[3] Acetylation of this compound with acetyl chloride in 1,2-dichloroethane in the presence of aluminum chloride gave a mixture of isomeric morphinans (Scheme I). The major isomer was easily separated from the mixture by fractional crystallization of its tartrate salt (mp 179–181 °C, yield 36%), and the minor isomer was isolated from the concentrated mother liquors (mp 188–190 °C, yield 19%). Tentatively, structures **8** (mp 179–181 °C) and **9** (mp 188–190 °C) were assigned to these substances, respectively. Conclusive identification of the isomers proved to be difficult simply by spectroscopic methods.

The isomers **8** and **9** had similar UV and IR spectra. The 100-MHz ^{1}H NMR spectrum of **8** ($CDCl_3$) features a characteristic ABX pattern for the three aromatic protons, namely, a one-proton doublet at δ 7.87 (J = 2 Hz), a one-proton doublet of doublets at 7.67 (J = 2 and 8 Hz),

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Table I. Physical and Biological Data

compd[d]	yield, %	mp or bp, °C (mm) (recryst solv)[a]	$[\alpha]^{25}_D$ (c, MeOH), deg	formula	anal.[b]	analgesic act.:[c-e] writhing	ED_{50}, mg/kg tail-flick
8	36	179–181 (A)	−6.10 (1.17)	$C_{19}H_{25}NO{\cdot}C_4H_6O_6$[f]	C, H, N	0.08 (0.07–0.10)[g]	4.0 (3.0–5.4)
9	19	188–190 (A)	−4.90 (1.01)	$C_{19}H_{25}NO{\cdot}C_4H_6O_6$[f]	C, H, N	4.0 (2.9–5.0)	>50
10	66	230–240 (0.1)	−127.21 (1.11)	$C_{21}H_{24}Cl_3NO_3$	C, H, N		
11	69	165–175 (0.1)	−24.77 (1.06)	$C_{18}H_{23}NO$	C, H, N		
12	66	263–265 (B)	−57.25 (0.98)	$C_{22}H_{29}NO{\cdot}HCl$	C, H, N	0.18 (0.13–0.23)	2.3 (1.8–4.5)
13	36	220–222 (C)	−54.43 (0.81)	$C_{23}H_{31}NO{\cdot}HCl$	C, H, N	1.2 (0.98–1.5)	4.9 (3.3–7.9)
14	74	100–102 (D)	−45.69 (1.08)	$C_{26}H_{31}NO{\cdot}C_4H_6O_6{\cdot}0.5H_2O$[f]	C, H, N	0.39 (0.25–0.51)	1.8 (1.5–2.4)
15	74	219–221 (D)	−30.00 (1.04)	$C_{19}H_{27}NO{\cdot}HCl$	C, H, N	0.24 (0.17–0.31)	1.3 (1.0–1.7)

[a] A = EtOH, B = $(Me)_2CO$–Et_2O, C = $(Me)_2CO$, D = EtOH–Et_2O. [b] Analyses of the elements indicated were within ±0.4% of theory. [c] The compounds were administered to the mice subcutaneously in distilled water for the writhing[9,10] and normal saline solution for the tail-flick[11,12] tests. [d] For biological data on the reference compounds, see Table II. [e] All biological tests were carried out on the salt indicated. [f] *d*-Tartrate. [g] Numbers in parentheses are the 95% confidence limits obtained by graphical[7] or regression[8] analysis.

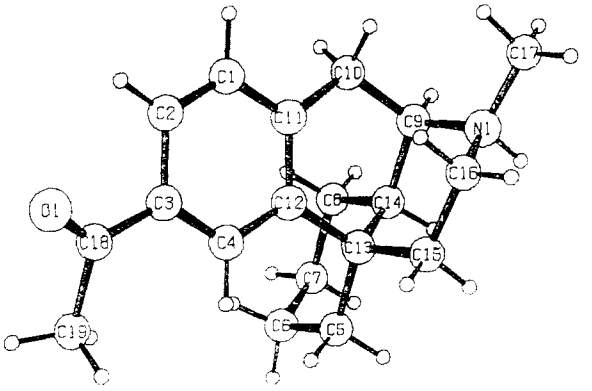


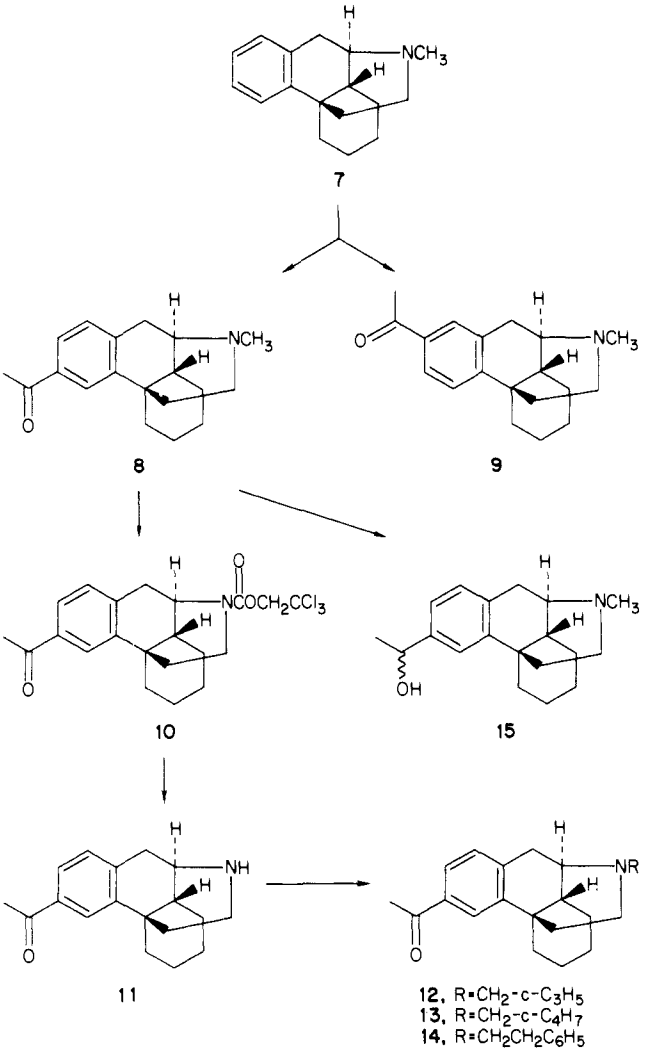
Figure 1. Structure of compound 8 as determined by X-ray analysis.

and a one-proton doublet at 7.18 (J = 8 Hz). This compound shows, among other signals, a three-proton singlet at δ 2.60 for the acetyl protons and a three-proton singlet for the *N*-methyl protons at 2.4.

On the other hand, the ^{1}H NMR spectrum in ($CDCl_3$) for **9** revealed an ABX system for the three aromatic protons, a one-proton broad singlet at δ 7.63, a one-proton broad doublet at 7.67, and a one-proton doublet at 7.25 (J = 8 Hz). The other important signals are a three-proton singlet at δ 2.49 for the acetyl protons and a three-proton singlet for the *N*-methyl protons at 2.31. Analysis of the ^{1}H NMR spectra of **8** and **9** confirmed the isomeric relationship, but the data were insufficiently characteristic to allow unambiguous structural assignments. Therefore, the structure and absolute configuration of the major isomer **8** was determined by X-ray analysis as shown in Figure 1. Since it has been shown by NMR that **9** is an isomer of **8**, it follows that the minor isomer has the structure and configuration shown in formula **9**.

(−)-3-Acetylmorphinan (**11**), a key intermediate for the synthesis of various N-substituted derivatives of this compound, was prepared from (−)-3-acetyl-*N*-methylmorphinan (**8**) (Scheme I). Reaction of **8** with 2,2,2-trichloroethyl chloroformate[4] in refluxing benzene followed by reduction of the resulting carbamate **10** with zinc in 90% acetic acid gave the nor compound **11**. Alkylation of **11** with cyclopropylmethyl chloride in dimethylformamide in the presence of potassium carbonate gave **12**, whereas alkylation with cyclobutylmethyl chloride and phenylethyl bromide under similar conditions afforded **13** and **14**, respectively. Finally, reduction of the ketone group in **8** with sodium borohydride in methanol gave a mixture of epimeric alcohols[5] (**15**). No attempt was made to separate these compounds. Compounds **8**–**15**, prepared in accordance with Scheme I, are compiled in Table I.

Scheme I



Results and Discussion

Tables I and II summarizes the results obtained in various test procedures[9–13] with the acylmorphinans **8**–**14**.

(4) Montzka, T. A.; Matiskella, J. D.; Partyka, R. A. *Tetrahedron Lett.* 1974, 1325.

(5) A 100-MHz NMR spectrum of the mixture in $CDCl_3$ in the presence of chiral shift reagent Eu(fod)$_3$ indicated a 1:1 mixture.

(6) Crystals of the perchlorate from **8** suitable for X-ray analysis were obtained by recrystallization from methanol.

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Table II. Analgesic Activities and Opiate Receptor Affinities

compd	route	analgesic act.:[a] ED_{50}, mg/kg writhing	analgesic act.:[a] ED_{50}, mg/kg tail-flick	binding affinities:[g,h] [^{3}]naltrexone (10^{-9} M) $10^{-6}IC_{50}$ (Tris buffer)
morphine[b]	sc	0.46 (0.26–0.83)[f]	4.06 (3.78–4.41)	0.027
	po	2.5 (1.40–4.45)	31.20 (26.30–35.73)	
codeine[c]	sc	2.3 (1.21–3.91)	38.97 (35.31–42.79)	10.0
	po	24.0 (13.71–42.00)	119.03 (105.16–132.21)	
levorphanol[d]	sc	0.11 (0.06–0.22)	1.21 (1.13–1.31)	0.004
	po	1.40 (0.70–2.80)	8.50 (7.22–10.25)	
8[d]	sc	0.08 (0.07–0.10)	4.0 (3.0–5.4)	0.21
	po	0.50 (0.32–0.66)	2.0 (1.6–2.4)	
9[d]	sc	4.0 (2.9–5.0)	>50	13.0
	po	22.3 (17.5–26.8)	75.0 (61.1–116.6)	
12[e]	sc	0.18 (0.13–0.23)	2.3 (1.8–4.5)	0.07
	po	2.1 (1.7–2.6)	1.5 (0.9–2.0)	
15[e]	sc	0.24 (0.17–0.31)	1.3 (1.0–1.7)	14.0
	po	0.36 (0.26–0.45)	1.1 (0.7–1.5)	

[a] The compounds were administered sc and po to the mice in distilled water for the writhing test[9,10] and in normal saline solution for the tail-flick test.[11,12] [b] Sulfate. [c] Phosphate. [d] Tartrate. [e] Hydrochloride. [f] Numbers in parentheses are the 95% confidence limits obtained by the graphic[7] or regression[8] analysis. [g] Binding was performed with rat brain homogenate. [h] Expressed as the concentration of compound required to inhibit stereospecific [^{3}H]naltrexone binding by 50%. The IC_{50} values are the means of results from three closely similar experiments.

Activities of these compounds were compared with those of morphine (1), codeine (2), and levorphanol (4). (−)-3-Acetyl-*N*-methylmorphinan (8), its *N*-cyclopropylmethyl analogue **12**, and the alcohol **15** derived from 8 were significantly more potent than morphine (1). When the acetyl group in 8 was displaced into the 2-position as in **9**, a significant decrease in analgesic activity was observed. Substituents on the nitrogen (**12–14**) have various effects on analgesic potency. Because of its favorable pharmacological properties, the (−)-3-acetyl-*N*-(cyclopropylmethyl)morphinan (**12**) was evaluated in other tests.

As shown in Table II, compound **12** interacted with the opiate receptor with an affinity comparable to that of morphine (1).[13,14] The oral analgesic potency of **12** is about 10 times that of codeine (2) in the writhing[9,10] and about 80 times as active in the tail-flick assay,[11,12] indicating good oral bioavailability. In order to obtain preliminary information on physical dependence liability, 8 and **12** were evaluated in the rat by continuous infusion. Studies with these compounds in rats made dependent upon morphine by continuous infusion (100 mg/kg per 24 h) for several days indicated that 8 substituted for morphine (1).[15] However, when **12** was substituted for morphine (1) and was infused continuously for 48 h at a dose of 100 mg/kg per 24 h, the rats lost just as much body weight and showed as many withdrawal signs and symptoms as did the morphine-dependent control rats that were subjected to abrupt morphine (1) withdrawal during this period. Thus, 100 mg/kg of **12** did not substitute for morphine (1). The very high dose of 200 mg/kg per 24 h of **12** did decrease the body weight loss and also reduced the number of withdrawal signs and symptoms, but this may not have been a true substitution since two of the five rats in this group expired at 72 h (i.e., 72 h after the continuous morphine (1) infusion ended, which was 24 h after infusion of **12** ended). It is conceivable that the relatively weak physical dependence liability of **12** is due to the *N*-cyclopropylmethyl moiety, which might confer antagonistic properties on this compound, as it does in the case of its phenolic analogue cyclorphan.[16] Interestingly, in an in vivo experiment in the mouse tail-flick test,[11,12] **12** did not antagonize the analgesic activity of morphine (1) [0.1 or 10 mg/kg of **12** oral and 10 mg/kg of morphine (1) subcutaneous]. Although the in vivo results did not support the possibility that **12** might have mixed agonist–antagonist properties, some in vitro results suggest such a profile. Thus, in an in vitro receptor-binding experiment in the presence of sodium ion as compared to the comparable concentration when sodium ion is omitted from the incubation mixture, the binding potency of **12** is decreased by 5.6-fold (IC_{50} changed from 7×10^{-8} to 4×10^{-7} M[14]). Since a "sodium response ratio" between 3 and 7 may be a predictor of agonist–antagonist properties,[17] it is conceivable that **12** might exhibit mixed properties. This result would be consistent with the finding[15] that **12** showed a relatively-low level of physical dependence liability in morphine-dependent rats. It seems probable, therefore, that binding of **12** to the opiate receptor may occur in a mode that is different from that of the phenolic morphinans and via the ketonic carbonyl group as one point of attachment.

In conclusion, pharmacological evaluation revealed that certain acylmorphinans are surprisingly potent analgesics and strongly bind to the opiate receptor in spite of the fact that they are not phenols or phenol derivatives. (−)-3-Acetyl-*N*-(cyclopropylmethyl)morphinan (**12**) is of special interest, since it is orally active and comparable in potency to morphine (1) in analgesic tests[9–13] and opiate receptor binding,[14] yet shows little or no physical dependence liability in morphine dependent rats.

Experimental Section

Chemistry. Melting points were taken in a Thomas-Hoover capillary melting point apparatus and are uncorrected. All compounds were characterized by IR (Beckman IR-9 spectro-

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(10) Hendershot, L. C.; Forsaith, J. *J. Pharmacol. Exp. Ther.* **1959**, *125*, 237.
(11) D'Amour, F. E.; Smith, D. L. *J. Pharmacol. Exp. Ther.* **1941**, *72*, 74.
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(15) Aceto, M. D., private communication.
(16) Harris, L. S.; Pierson, A. K.; Dembinski, J. R.; Dewey, W. L. *Arch. Int. Pharmacodyn.* **1967**, 165.
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Table III. Summary of Crystal Data for Compound 8

formula	$C_{19}H_{25}NO \cdot HClO_4$[a]
formula wt	383.87
space group	$P2_12_12_1$
a, Å	7.458 (6)
b, Å	10.413 (8)
c, Å	24.42 (2)
Z	4
d_{calcd}, g cm^{-3}	1.344 g
μ(Cu Kα), cm^{-1}	20.5

[a] Reference 6.

photometer), UV (Cary 14-spectrophotometer), and NMR (Varian Associates A-60 and HA-100 spectrometers, Me_4Si internal standard). Specific rotation measurements were performed on a Perkin-Elmer 141 electronic polarimeter. Where analyses are indicated by symbols of the elements, results obtained were within ±0.4% of theoretical values.

(−)-3- and 2-Acetyl-*N*-methylmorphinan (8 and 9) *d*-Tartrate. To a rapidly stirred slurry of 44.0 g (0.33 mol) of $AlCl_3$ in 450 mL of 1,2-dichloroethane at 0 °C was added portionwise over 15 min 37.0 g (0.13 mol) of **7**·HCl. To this mixture was added dropwise a solution of 20.1 g (0.26 mol) of freshly distilled acetyl chloride in 15 mL of 1,2-dichloroethane. The mixture was refluxed for 3 h, cooled, and poured onto 800 mL of ice-water. The aqueous suspension was made alkaline with 10 N NaOH and extracted with two 1-L portions of $CHCl_3$. The combined extracts were washed with 500 mL of H_2O, dried over $MgSO_4$, and concentrated to give 26.9 g (70%) of a crude mixture of isomeric morphinans **8** and **9**. A hot solution of 26.9 g (0.09 mol) of the mixture of **8** and **9** in 100 mL of EtOH (2B) was combined with a hot soluton of 15.0 g (0.1 mol) of *d*-tartaric acid in 100 mL of EtOH (2B) and the resulting mixture allowed to crystallize at room temperature for 24 h. The crystals were collected and recrystallization from EtOH afforded 14.8 g (36%) of **8**·$C_4H_6O_6$. The filtrates obtained in the separation of **8**·$C_4H_6O_6$ were concentrated to a volume of about 100 mL and then warmed on the stream bath until a clear solution was obtained and allowed to crystallize at room temperature for 7 days. The resulting salts were collected and recrystallized three times from EtOH to give 7.8 g (19%) of **9**·$C_4H_6O_6$.

2,2,2-Trichloroethyl (−)-3-Acetylmorphinan-*N*-carboxylate (10). After a mixture of 2.7 g (0.01 mol) of **8**, 20 mg of K_2CO_3, and 2.11 g (0.01 mol) of 2,2,2-trichloroethyl chloroformate in 10 mL of benzene had been heated under reflux for 48 h, it was washed with two 30-mL portions of 1 N HCl, dried over $MgSO_4$, and concentrated to give 2.8 g (66%) of **10**.

(−)-3-Acetylmorphinan (11). To a solution of 2.4 g (0.005 mol) of **10** in 40 mL of 90% HOAc was added portionwise 2.2 g of zinc dust and the mixture was stirred for 16 h at room temperature. After removal of the zinc by filtration, the filtrate was concentrated in vacuo and the residue was partitioned between 40 mL of Et_2O and dilute NH_4OH. The Et_2O solution was extracted with 60 mL of 4 N HCl and the acid extract was made alkaline with concentrated NH_4OH and extracted with two 30-mL portions of Et_2O. The combined organic extracts were dried over $MgSO_4$ and concentrated to give 1.0 g (69%) of **11** as a viscous oil.

(−)-3-Acetyl-*N*-(cyclopropylmethyl)morphinan (12) Hydrochloride. To a mixture of 0.8 g (0.003 mol) of **11**, 0.6 g of K_2CO_3, and 10 mL of DMF was added 0.30 g (0.003 mol) of cyclopropylmethyl chloride. After the mixture had been heated at reflux for 16 h, it was cooled to room temperature and filtered. Evaporation of the DMF, dissolution of the residue in Et_2O, washing with H_2O, drying over $MgSO_4$, filtration, and evaporation of the Et_2O gave the crude base **12**. The base on treatment with EtOAc–HCl in EtOAc gave 0.70 g (66%) of **12**·HCl.

(−)-3-Acetyl-*N*-(cyclobutylmethyl)morphinan (13) Hydrochloride. Reaction of 1.7 g (0.006 mol) of **11** with 1.2 g (0.01 mol) of cyclobutylmethyl chloride in 40 mL of DMF containing 1.5 g of K_2CO_3 using the reaction conditions given for **12** produced the crude base **13**, which on treatment with EtOAc–HCl in EtOAc gave 0.84 g (36%) of **13**·HCl.

Table IV. Summary of Experimental Details for Crystallographic Analysis of Compound 8

crystal size, mm	0.10 × 0.18 × 0.65
maximum θ, deg	57
no. of obsd refln	1345
absorption correction	yes
least-squares refinement	full matrix
heavier atoms	anisotropic
H atoms	isotropic
final R	0.086
final R_w	0.101
final difference map largest peak, e Å^{-3}	<±0.7

(−)-3-Acetyl-*N*-phenethylmorphinan (14) *d*-Tartrate Hemihydrate. The procedure similar to that for **12** was followed. Treatment of 1.5 g (0.005 mol) of **11** with 1.3 g (0.007 mol) of (2-bromoethyl)benzene in 40 mL of DMF containing 1.1 g of K_2CO_3 gave the crude base **14**. The base on treatment with *d*-tartaric acid in EtOH gave 2.2 g (74%) of **14**·$C_4H_6O_6$ as the hemihydrate.

(−)-α,*N*-Dimethylmorphinan-3-methanol (15) Hydrochloride. To a stirred solution of 3.0 g (0.01 mol) of **8** in 50 mL of MeOH was added portionwise 3.0 g (0.08 mol) of $NaBH_4$ and the mixture was stirred at room temperature for 16 h. The solvent was removed under reduced pressure and the residue was partitioned between H_2O and Et_2O. The ether solution was washed with H_2O, dried over $MgSO_4$, and concentrated in vacuo to give an epimeric mixture[5] of the crude base **15**. The base on treatment with EtOAc–HCl in EtOAc afforded 2.5 g (74%) of **15**·HCl.

Crystallography. All intensity data were measured on a Hilger-Watts diffractometer (Ni-filtered Cu Kα radiation, θ–2θ scans, pulse height discrimination). The crystal data are given in Table III. A multiple solution procedure[18] was used to solve the structure. Experimental details are summarized in Table IV.

Pharmacological Results. Analgesic potencies were determined by both the tail-flick[11,12] and the phenylquinone writhing methods.[9,10] The results are presented in Tables I and II.

Binding assays were performed in rat brain homogenates as previously described.[13] The concentration of test compound necessary to displace half of the stereospecific [^{3}H]naltrexone binding (IC_{50}) is shown in Table II.[14]

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Registry No. **7**·HCl, 85619-62-1; **8**, 85619-65-4; **8**·$C_4H_6O_6$, 85619-66-5; **9**, 85619-63-2; **9**·$C_4H_6O_6$, 85619-64-3; **10**, 85619-87-0; **11**, 85632-84-4; **12**, 85619-68-7; **12**·HCl, 85619-69-8; **13**, 85619-70-1; **13**·HCl, 85619-71-2; **14**, 85619-74-5; **14**·$C_4H_6O_6$, 85619-75-6; **15** (isomer 1), 85619-89-2; **15** (isomer 2), 85619-88-1; 15-HCl (isomer 1), 97012-75-4; **15**·HCl (isomer 2), 97012-76-5; cyclobutylmethyl chloride, 78415-89-1; acetyl chloride, 75-36-5; trichloroethyl chloroformate, 17341-93-4; cyclopropylmethyl chloride, 5911-08-0; (2-bromoethyl)benzene, 103-63-9.

Supplementary Material Available: Tables V and VI, the bond lengths and angles in compound **8**; Tables VII and VIII, the final atomic and anisotropic thermal parameters for compound **8** (4 pages). Ordering information is given on any current masthead page.

(18) Germain, G.; Main, P.; Woolfson, M. M. *Acta Crystallogr., Sect. A* 1971, *A27*, 368.